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S.G. Holtzman "Life Sciences", volume 16, published 1975, by Pergamon Press (Oxford, New York, Braunschweig), see pages 1465-1470, especially page 1465, second passage, page 1466, sixth passage, page 1467, last passage, page 1468, fig. 1, fourth passage, lasr passage of the discussion

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Description

One of the basic phenomena of life is that living creatures take food from their environment. This basic phenomenon has arisen simultaneously with the rise of life. Considering that for the living creatures both overfeeding and underfeeding are dangerous, simultaneously with the rise of the food intake, also a system for controlling the food intake has arisen. Together with the development of life, this system also became more and more developed, and today it operates as a very complicated system "having several regulating circles". (A summary of some presumed and proved regulating mechanisms is given in The Lancet of February 19, 1983 on pages 398 to 401). One of these regulating mechanisms is based on the so-called opioid endogenic peptides. This is supported by the observation that if a special opiate antagonist, naloxone [(5α)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-morphinane-6-one] is administered to animals it is absorbed by the opiate receptors and thereby the food intake, the appetite and also the fluid intake of the animal is hindered. The observation that by the administration of endogenic (and exogenic) opiates the appetite of animals and humans can be increased shows that these compounds exert an influence on the nutrition (Am. J. Clin. Nutr., *35*, 757—761, 1982 and Appetite, *2*, 193—208, 1981).

While in case of non-domestic animals the regulating mechanisms function more or less properly and ensure the appropriate food intake of the animals, in case of humans often lesions deriving from overfeed emerge.

This can be readily understood, as on the one hand human food intake is caused not only by the sensation of hunger and, on the other hand the degree of the food intake does not follow the demands of the organism, the demands are often many time surpassed. It is true that by purposeful food intake obesity can be avoided, but in many instances the decision in itself is not sufficient for changing the alimentary habits, and for carrying out the decision a medical support is necessary as well.

The best known slimming agents are desopimone (4-chloro-α,α-dimethyl-phenethylamine), gracidine (3-methyl-2-phenyl-morpholine) and teronac [5-(p-chlorophenyl)-2,5-dihydro-3H-imidazo[2,1-*a*]isoindole-5-ol).

Unfortunately the known slimming agents have several contraindications and side effects, so for a great part of the patients requiring treatment these agents cannot be used.

The side effects of desopimone are the dilatation of the pupil, increase of the inner pressure of the eyes, vomiting, diarrhoea, abdominal pains, difficulty at the beginning of urination, headache, allergic exanthema, vertigo; and insomnia and nervosity as well as somnolence and sedative effect appear in about equal proportions.

Gracidine can only be administered with increased care in the case of obesity associated with heart diseases, cardiovascular troubles and hypertension. At the intake of gracidine and whent it is administered continuously during the treatment, driving of vehicles, working above ground and on dangerous machines are prohibited. During its use the consumption of alcoholic drinks is prohibited. According to new information the compositions containing gracidine are forbidden.

Teronac may cause mouth dryness, headache, nervosity, nausea, constipation, impairment of sleep, dizziness, tachycardia, disturbance of sexual functions, sweating, eczema, dilatation of the pupil and allergy. Also in case of glaucoma, heart-rhythm troubles, serious cardiac failure, renal insufficiencies, liver troubles, hypertension, cerebral processes, psychiatric diseases, gastric and intestinal ulcers it is contraindicated.

On the basis of the aforesaid an appetite reducing composition is needed which does not show the side effects of the known compositions and which can be widely used without side effects.

As the active ingredients of a composition those substances can be taken into consideration which exert their influence on the field of the central nervous system. Substances of this type are also the opiate antagonists mentioned above.

It is known that on obese people the food intake is reduced by naloxone (J. Clin. Endocrin. Metab., *55*, 196—198, 1982). It has the similar activity in Prader-Willi syndrome (The Lancet, 1980, 876—877), traumatic hypothalamic hyperphagia (Am. J. Clin. Nutr., *35*, 757—761, 1982) and also in case of healthy patients rendered hungry by 2-desoxy-glucose infusion.

The use of naloxone as active ingredient in appetite reducing compositions is unadvisable, particularly by the fact that when administered per os it should be given in extremely high doses. But in case of a widely used appetite reducing composition only peroral administration can come into consideration.

The object of the present invention is to provide an appetite reducing composition which can be widely used without side effects and contraindications.

Brief description of the invention

The object of the present invention is attained by an appetite reducing composition containing as active ingredient nalorphine [(5α, 6α)-7,8-didehydro-4,5-epoxy-17-(2-propenyl)-morphinane-3,6-diol]. This composition can be administered perorally.

Detailed description of the invention

The present invention concerns that use of (5α, 6α)-7,8-didehydro-4,5-epoxy-17-(2-propenyl)-morphinane-3,6-diol i.e. nalorphine, or a salt thereof formed with a strong acid, for the manufacture of oral

medicaments for reducing appetite. Preferably nalorphine is in the form of its salt prepared with a strong acid, such as a mineral acid, e.g., hydrochloric acid and hydrobromic acid. It is formulated into pharmaceutical compositions with carriers, diluents, flavouring, aromatizing, colouring agents and other auxiliary materials normally used for the preparation of oral pharmaceutical compositions.

The pharmaceutical compositions of the present invention are prepared in the form of tablets, dragées, pilules, encapsulated powder compositions and various solutions, and suspensions (such as liquid medicines and drops).

According to a preferred embodiment of the invention one dosage unit or a low number of the dosage units (tablet, dragée, capsule, drop or spoonful amount) of the pharmaceutical composition contain the single dose. A dosage unit may contain of course more doses, in this case for example the tablets may be provided with dividing cuts in order to facilitate breaking them into pieces.

The daily dose of the active ingredient is 5 to 30 mg. As the active ingredient is known as an antinarcotic, the actual dose can be easily determined by the physician on the basis of his skill, considering the individual reactivity and tolerance of the patient and the effect intended to be achieved. These doses may exceed the doses mentioned above or may be less than indicated. The daily dose may be divided into more single doses containing equal or different amounts of the active ingredient. Thus the constant active ingredient level can be easily ensured.

It has been surprisingly found, that during or after the treatment carried out with the pharmaceutical composition of the present invention, the side effect of mouth dryness attributable to the composition was only observed very rarely and in a very mild form. No side effect was observed which could have been connected to the narcotic effect of the opium derivatives. No dependence on the medicine has been risen, no habituation or withdrawal symptoms were observed after the treatment.

The invention is illustrated by the following non limiting examples.

Example 1

Tablet containing 5 mg of active ingredient

A powder mixture of the following composition is prepared:

Nalorphine hydrobromide	5.0 g
Colloidal silica	1.0 g
Magnesium stearate	3.0 g
Talc	9.0 g
Microcrystalline cellulose	82.0 g
	100.0 g

From the powder mixture thus obtained after homogenisation, tablets each weighing 100.00 mg are compressed under a pressure of 49—785 MPa (500—8000 kp/cm^2).

Example 2

Tablet containing 1 mg of active ingredient

A powder mixture of the following composition is prepared:

Nalorphine hydrobromide	10.0 g
Colloidal silica	1.0 g
Magnesium stearate	3.0 g
Talc	9.0 g
Microcrystalline cellulose	77.0 g
	100.0 g

From the powder mixture thus obtained after homogenisation tablets each weighing 100.00 mg are compressed under a pressure of 49—785 MPa (500—8000 kp/cm^2).

Example 3

Tablet containing 20 mg of active ingredient

A powder mixture of the following composition is prepared:

Nalorphine hydrobromide	20.0 g
Talc	3.0 g
Magnesium stearate	4.0 g
Mannitol	108.0 g
	135.0 g

From 15.0 g of starch and water a 3—5% granulating liquid is prepared. The powder mixture is granulated with the starch solution thus obtained. Granules having a diameter of 1 mm are prepared. The granules are dried at a temperature of 50°C, then they are compressed under a pressure of 49—785 MPa (500—8000 kp/cm^2) into tablets each weighing 150.00 mg.

Clinical tests were carried out on obese voluntary patients with the tablets containing 5 mg of active ingredient prepared according to Example 1. The body weight was measured at the beginning and at the end of the test, the number of the tablets administered daily was also registered and at the end of the treatment the weight loss was calculated as kg/week. The following Table contains the data thus obtained together with the occasional side effects.

TABLE

Number of patient	Body weight		Weight loss (kg/week)	Number of tablets per day	Side effect
	at admission	at discharge			
1.	103.5 kg	100.5 kg	0.75	2	Mouth dryness
2.	92.0 kg	84.5 kg	1.07	1	Ø
3.	82.0 kg	76.0 kg	0.50	3	Ø
4.	80.0 kg	78.0 kg	0.66	3	Ø
5.	123.0 kg	122.0 kg	0.50	5	Ø
6.	87.0 kg	85.0 kg	1.0	3	Ø
7.	80.0 kg	77.0 kg	0.75	2	Ø
8.	84.0 kg	79.0 kg	0.83	2	Ø
9.	114.0 kg	108.0 kg	0.75	3	Obstipation
10.	78.0 kg	72.0 kg	1.0	4	Thirst
11.	100.0 kg	87.0 kg	2.1	3	Obstipation
12.	90.0 kg	82.0 kg	0.5	4	Obstipation
13.	114.0 kg	98.0 kg	0.7	3	Obstipation
14.	92.0 kg	81.5 kg	0.7	4	Obstipation
15.	124.0 kg	108.0 kg	0.8	3	Ø
16.	97.0 kg	88.0 kg	0.4	5	Ø
17.	75.0 kg	68.0 kg	0.7	6	Transitorial vertigo
18.	103.0 kg	99.0 kg	0.5	5	Ø
19.	83.0 kg	75.0 kg	1.0	4	Transitorial nausea
20.	96.0 kg	77.0 kg	1.1	3	Obstipation
21.	91.0 kg	87.0 kg	0.5	4	Ø
22.	86.0 kg	75.0 kg	1.5	5	Obstipation
23.	104.0 kg	93.0 kg	0.5	4	Ø

TABLE (Cont.)

Number of patient	Body weight at admission	Body weight at discharge	Weight loss (kg/week)	Number of tablets per day	Side effect
24.	78.0 kg	72.0 kg	0.7	4	Ø
25.	109.0 kg	100.0 kg	0.9	4	Obstipation
26.	119.0 kg	106.0 kg	1.0	4	Ø
27.	97.3 kg	87.3 kg	1.0	4	Ø
28.	82.5 kg	76.0 kg	0.6	3	Ø
29.	126.2 kg	115.0 kg	1.3	3	Obstipation
30.	81.5 kg	73.8 kg	1.1	3	Ø
31.	83.0 kg	75.0 kg	0.8	3	Obstipation
32.	108.6 kg	101.3 kg	0.8	3	Transitorial vertigo sleepiness
33.	119.8 kg	112.0 kg	0.8	4	Obstipation
34.	115.0 kg	110.5 kg	0.9	4	Obstipation
35.	98.0 kg	87.0 kg	1.2	3	Ø
36.	97.0 kg	90.0 kg	1.1	3	Ø
37.	115.5 kg	100.3 kg	2.1	3	Ø
38.	125.0 kg	102.5 kg	1.3	3	Ø
39.	132.0 kg	121.0 kg	0.7	4	Ø

Claims

1. Use of (5α, 6α)-7,8-didehydro-4,5-epoxy-17-(2-propenyl)-morphinane-3,6-diol i.e. nalorphine, or a salt thereof formed with a strong acid, for the manufacture of oral medicaments for reducing appetite.

2. Use according to Claim 1, characterized in that solid pharmaceutical compositions, preferably tablets, are prepared using solid auxiliary materials.

3. Use according to Claim 1 or 2, characterized in that 5 to 30 mg of nalorphine, or a salt thereof formed with a strong acid, are used per dosage unit.

4. Use according to Claim 2 or 3, characterized in that one or more of the following auxiliary materials:
—silica,
—magnesium stearate,
—talc
—microcrystalline cellulose, and
—mannitol
are further used.

5. Use of nalorphine hydrobromide for the manufacture of an oral tablet for reducing appetite, which contains:
—5.0 mg of nalorphine hydrobromide,
—1.0 mg of colloidal silica,
—3.0 mg of magnesium stearate,
—9.0 mg of talc, and
—82.0 mg of microcrystalline cellulose.

6. Use of nalorphine hydrobromide for the manufacture of an oral tablet for reducing appetite, which contains:
—10.0 mg of nalorphine hydrobromide,
—1.0 mg of colloidal silica,
—3.0 mg of magnesium stearate,
—9.0 mg of talc, and
—77.0 mg of microcrystalline cellulose.

7. Use of nalorphine hydrobromide for the manufacture of an oral tablet for reducing appetite which contains:
—20.0 mg of nalorphine hydrobromide,
—3.0 mg of talc,
—4.0 mg of magnesium stearate, and
—108.0 mg of mannitol.

Patentansprüche

1. Verwendung eines (5α, 6α)-7,8-didehydro-4,5-epoxy-17-(2-Propenyl)-Morphinan-3,6-Diol i.e. Nalorphine oder eines deren mit einer starken Säure gebildeten Salze zur Herstellung eines oralen Medikamentes zur Appetitreduzierung.

2. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß feste, pharmazeutische Zusammensetzungen, vorzugsweise Tabletten, unter Benutzung fester Hilfsmaterialien hergestellt werden.

3. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß 5 bis 30 mg von Nalorphin oder eines deren mit einer starken Säure gebildeten Salz pro Dosierungseinheit eingesetzt werden.

4. Verwendung nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß eine oder mehrere der folgenden Hilfsmaterialien darüber hinaus eingesetzt werden: Siliciumdioxid (silicia), Magnesium-Stearate, Talg, mikrokristalline Zellulose und Mannit (Mannitol).

5. Verwendung von Narphin-Hydrobromid für die Herstellung einer oralen Tablette zur Appetitreduzierung
—0,5 mg Narphin-Hydrobromid,
—1,0 mg kollodiales Siliciumdioxid,
—3,0 mg Magnesium-Stearat,
—9,0 mg Talg und
—82,0 mg mikrokristalline Zellulose
enthält.

6. Verwendung von Narphin-Hydrobromid für die Herstellung einer oralen Tablette zur Appetitreduzierung
—10,0 mg Narphin-Hydrobromid,
—1,0 mg kollodiales Siliciumdioxid,
—3,0 mg Magnesium-Stearat,
—9,0 mg Talg und
—77,0 mg mikrokristalline Zellulose
enthält.

7. Verwendung von Narphin-Hydrobromid für die Herstellung einer oralen Tablette zur Appetitreduzierung
—20,0 mg Narphin-Hydrobromid,
—3,0 mg Talg
—4,0 mg Magnesium-Stearat und
—108,0 mg Mannitol
enthält.

Revendications

1. Utilisation du (5α, 6α)-7,8-didéhydro-4,5-époxy-17-(2-propényl)-morphinane-3,6-diol, c'est-à-dire de la nalorphine, ou d'un sel de ce composé formé avec un acide fort, pour la fabrication de médicaments oraux pour réduire l'appétit.

2. Utilisation selon la revendication 1, caractérisée en ce que des compositions pharmaceutiques solides, de préférence des comprimés, sont préparées en utilisant des matières adjuvantes solides.

3. Utilisation selon la revendication 1 ou 2, caractérisée en ce que 5 à 30 mg de nalorphine, ou d'un sel de ce composé, formé avec un acide fort, sont utilisés par dose d'administration.

4. Utilisation selon la revendication 2 ou 3, caractérisée en ce que l'une ou plusieurs des matières adjuvantes suivantes:
—silice,
—stéarate de magnésium,
—talc,
—cellulose microcristalline, et

—mannitol

sont en outre utilisées.

5. Utilisation du bromhydrate de nalorphine pour la fabrication d'un comprimé oral pour réduire l'appétit, qui contient:

—5,0 mg de bromhydrate de nalorphine,
—1,0 mg de silice colloïdale,
—3,0 mg de stéarate de magnésium,
—9,0 mg de talc, et
—82,0 mg de cellulose microcristalline.

6. Utilisation du bromhydrate de nalorphine pour la fabrication d'un comprimé oral pour réduire l'appétit, qui contient:

—10,0 mg de bromhydrate de nalorphine,
—1,0 mg de silice colloïdale,
—3,0 mg de stéarate de magnésium,
—9,0 mg de talc, et
—77,0 mg de cellulose microcristalline.

7. Utilisation du bromhydrate de nalorphine pour la fabrication d'un comprimé oral pour réduire l'appétit, qui contient:

—20,0 mg de bromhydrate de nalorphine,
—3,0 mg de talc,
—4,0 mg de stéarate de magnésium et
—108,0 mg de mannitol.